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Long-Term Survival and Late Effects among One-Year Survivors of Second Allogeneic Hematopoietic Cell Transplantation for Relapsed Acute Leukemia and Myelodysplastic Syndromes

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A B S T R A C T

We analyzed the outcomes of patients who survived disease-free for 1 year or more after a second allogeneic hematopoietic cell transplantation (HCT) for relapsed acute leukemia or myelodysplastic syndromes between 1980 and 2009. A total of 1285 patients received a second allogeneic transplant after disease relapse; among these, 325 were relapse free at 1 year after the second HCT. The median time from first to second HCT was 17

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and 24 months for children and adults, respectively. A myeloablative preparative regimen was used in the second transplantation in 62% of children and 45% of adult patients. The overall 10-year conditional survival rates after second transplantation in this cohort of patients who had survived disease-free for at least 1 year was 55% in children and 39% in adults. Relapse was the leading cause of mortality (77% and 54% of deaths in children and adults, respectively). In multivariate analyses, only disease status before second HCT was significantly associated with higher risk for overall mortality (hazard ratio, 1.71 for patients with disease not in complete remission before second HCT, $P < .01$). Chronic graft-versus-host disease (GVHD) developed in 43% and 75% of children and adults after second transplantation. Chronic GVHD was the leading cause of nonrelapse mortality, followed by organ failure and infection. The cumulative incidence of developing at least 1 of the studied late effects within 10 years after second HCT was 63% in children and 55% in adults. The most frequent late effects in children were growth disturbance (10-year cumulative incidence, 22%) and cataracts (20%); in adults they were cataracts (20%) and avascular necrosis (13%). Among patients with acute leukemia and myelodysplastic syndromes who receive a second allogeneic HCT for relapse and survive disease free for at least 1 year, many can be expected to survive long term. However, they continue to be at risk for relapse and nonrelapse morbidity and mortality. Novel approaches are needed to minimize relapse risk and long-term transplantation morbidity in this population.

INTRODUCTION

Disease relapse is the leading cause of treatment failure after allogeneic hematopoietic cell transplantation (HCT) for hematologic malignancy and occurs in approximately 20% to 60% of patients [1-5]. The outcome after disease relapse after first transplantation is poor, with survival rates less than 10% in some populations, and treatment options for these patients are limited [5-8]. Second HCT is a potentially curative option for selected patients and disease relapse is the most common indication for second allogeneic transplantation [9]. The decision to undergo a second transplantation is complex, given the heightened risks of disease recurrence, acute toxicity, post-transplantation late effects, and transplantation-related mortality.

Rates of overall survival after second allogeneic HCT range between 28% and 60%, with disease-free survival rates of 25% to 56% [1,2,9-15]. Studies of second transplantation in children have demonstrated more favorable survival, but are limited by small patient numbers [11,16]. Previous studies of second transplantation have been limited in sample size and, hence, have been inconsistent in identifying favorable factors for longer survival after second allogeneic HCT. Notwithstanding the limitation of small sample size, factors associated with superior survival include younger recipient age, longer duration of remission between transplantations, complete remission (CR) at second transplantation, bone marrow as the stem cell source, the use of a fully HLA-matched donor, the presence of acute and chronic graft-versus-host disease (GVHD), and transplant from a female donor [1,9-12,17,18]. An area of controversy has been the impact of the intensity of conditioning regimen on survival, as some studies have found reduced-intensity conditioning regimens to favorably impact survival, whereas others found survival to benefit from high-dose myeloablative regimens containing total body irradiation [2,12,15]. An additional area of discussion is the impact of using the same or alternate donor with the second transplantation.

Much attention has been paid to analyzing late effects after single allogeneic HCT. The Bone Marrow Transplant Survivor Study reported that 66% to 79% of long-term survivors of HCT suffered from at least 1 chronic health condition [19-21]. The rates of long-term survival and the incidence of late effects after second allogeneic transplantation have not been well described. Given the cumulative exposure to chemotherapy and radiation, recipients of 2 or more transplants may be at substantial risk for late complications.

In this study, we selected a cohort of patients who were alive and in remission for 1 year or more after a second allogeneic HCT for relapsed acute leukemia or myelodysplastic syndrome (MDS) to describe: (1) long-term survival and predictive factors for survival outcomes, and (2) cumulative incidence of late effects in this population.

MATERIALS AND METHODS

Data Source and Patients

Data for this study were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on hematopoietic cell transplantations to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program in Minneapolis. Participating centers are required to report all transplantation consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Data are collected before transplantation, 100 days and 6 months after transplantation, and annually thereafter, or until death. Observational studies conducted by the CIBMTR are performed under guidance of the institutional review board of the National Marrow Donor Program and are in compliance with all applicable federal regulations pertaining to the protection of human research participants.

Transplantation-essential data are collected for all patients participating in CIBMTR data collection. These includes demographic, disease type and stage, survival, relapse, graft type, the presence of GVHD, and cause of death data. A subset of CIBMTR participants are selected for comprehensive research level data collection by weighted randomization. Late effects data are collected from this group of patients. Transplantation centers report the presence of clinically significant organ impairment or disorder at 6 months and 1 year after transplantation and annually thereafter. Centers are specifically asked to report the presence of the following late effects: stroke/seizure, myocardial infarction, cirrhosis, gonadal dysfunction requiring hormone replacement, renal failure severe enough to warrant dialysis, avascular necrosis, cataracts, growth hormone deficiency/growth disturbance, hypothyroidism, and bronchiolitis obliterans.

Study Population

The study population included children (age $\leq$ 18 years) and adults (age $>$ 18 years) who had survived disease free for at least 1 year after their second allogeneic HCT for acute lymphoblastic leukemia, acute myelogenous leukemia, juvenile myelomonocytic leukemia (JMML), and MDS between January 1, 1980 and December 31, 2009. There was no exclusion based on type of conditioning regimen. The intensity of the conditioning regimen was based on the definitions published by Bacigalupo et al. [22]. All types of donor grafts were included with the exception of syngeneic twins. Patients who had an allogeneic HCT after autologous transplantation were not included in the analysis.

Among the 2129 second allogeneic HCT reported to the CIBMTR for patients with acute lymphoblastic leukemia, acute myelogenous leukemia, JMML, and MDS during the study time period, 1285 (63%) transplantation were performed for disease relapse. Other indications for second HCT were nonengraftment or graft failure (31%) and new malignancy (1%). The reason for second transplantation was unknown for 5% of the population. Among those who underwent transplantation for disease relapse, 952 (74%) patients died or experienced disease relapse in the first year after the second transplantation. From the 333 remaining patients, 8 were further excluded because of an unknown graft type. The final study cohort consisted of 325 second transplant recipients who had survived in remission for at least 1 year after the second transplantation.

Statistical Analysis

Descriptive statistics were used to describe patient demographic, disease, and HCT-related variables. All outcomes were evaluated, unless clarified, by calculating the probability of that outcome after second

Table 1
Patient and Transplantation Characteristics

Characteristics at Second HCT	Age at Second Transplantation	
	Children (≤18 years) n (%)	Adults (>18 years) n (%)
No. of patients	146	179
No. of centers	71	92
Male/female	92 (63)/54 (37)	99 (55)/80 (45)
Disease		
Acute myeloid leukemia	64 (44)	111 (62)
Acute lymphoblastic leukemia	66 (45)	54 (30)
MDS	12 (8)	14 (8)
JMML	4 (3)	0
Patient age at first transplantation, median (range), yr	7 (<1-16)	35 (14-66)
Patient age at second transplantation, median (range), yr	9 (1-17)	38 (19-66)
Lansky/Karnofsky score ≥ 90	101 (69)	96 (54)
Donor type		
HLA-matched sibling	78 (53)	99 (55)
Other related	8 (5)	8 (4)
Unrelated	60 (41)	72 (40)
Graft type		
Bone marrow	94 (64)	63 (35)
Peripheral blood stem cells	34 (23)	113 (63)
Umbilical cord blood	18 (12)	3 (2)
Disease status before first HCT*		
Early	67 (46)	90 (50)
Intermediate	49 (34)	35 (20)
Advanced	26 (18)	54 (30)
Unknown	4 (3)	0
Disease remission status before second HCT		
Complete remission	108 (74)	88 (49)
Relapse/progression	29 (20)	77 (43)
Unknown	9 (6)	14 (8)
Interval from first HCT to relapse, median (range), mo	14 (<1-145)	18 (<1-157)
<12 months	67 (46)	64 (36)
12-23 months	42 (29)	44 (25)
≥24 months	37 (25)	71 (40)
Interval from first HCT to second HCT, median (range), mo	17 (2-149)	24 (2-158)
<12 months	46 (32)	41 (23)
12-23 months	48 (33)	49 (27)
≥24 months	52 (36)	89 (50)
First HCT and second HCT donor pair		
Same related donor	72 (50)	80 (45)
Different related donor	8 (6)	21 (12)
Related donor − unrelated donor	9 (6)	7 (4)
Related donor − donor relationship unknown	4 (2)	3 (2)
Same unrelated donor	15 (10)	26 (15)
Different unrelated donor	27 (18)	33 (18)
Unrelated donor − related donor	3 (2)	3 (2)
Unrelated, donor − donor relationship unknown	9 (6)	6 (3)
Conditioning regimen intensity for first HCT		
Myeloablative	130 (89)	141 (79)
Reduced intensity	5 (3)	33 (18)
Conditioning regimen intensity for second HCT		
Myeloablative	90 (62)	81 (45)
Reduced intensity	38 (26)	73 (41)
None	5 (3)	12 (7)
Unknown	5 (3)	12 (7)
Year of second HCT		
1980-1989	14 (10)	20 (11)
1990-1999	67 (45)	53 (30)
2000-2009	65 (45)	106 (59)

* Disease status classification: early-risk disease included acute leukemia in first complete remission, myelodysplastic syndrome, refractory anemia, or refractory anemia with ringed sideroblasts, or unspecified myelodysplastic syndrome with pretransplantation marrow blasts <5%; intermediate-risk disease included acute leukemia in second or greater complete remission; advanced-risk disease included acute leukemia in relapse or primary induction failure, myelodysplastic syndrome, refractory anemia with excess blasts or excess blasts in transformation or marrow blasts >5%, and juvenile myelomonocytic leukemia.

transplantation conditioned upon the fact that the patient had survived and remained disease free for at least 1 year after the second transplantation. The Kaplan-Meier method was used to estimate the probability of survival. The cumulative incidence function was used to estimate relapse-related death, nonrelapse mortality, and late effects. Rates of individual late effects occurring between the first and second HCT were calculated. Rates of individual late effects were calculated after first HCT (censored at second transplantation). Cumulative incidences of late effects and probabilities of other outcomes were estimated for 2 and 10 years after the second HCT and are reported separately for children and adult survivors. A proportional hazards model was developed to assess risk factors for the conditional risk of overall mortality among the study population. Potential risk factors considered include age, separately among children and adults as well as children versus adults, diagnosis category, disease status at first and second transplantation (CR versus relapse/progressive disease/partial remission), first-second transplantation donor pair (related-related versus related-unrelated versus unrelated-unrelated, same donor versus unrelated-unrelated, different donor versus other), development of GVHD before second transplantation (none versus acute GVHD alone versus acute GVHD and chronic GVHD), interval between first and second transplantations, and conditioning intensity at second transplantation (myeloablative versus nonmyeloablative/reduced intensity). Patients with JMML were excluded from the proportional hazard model because of small patient numbers. Proportional hazards models were not developed to assess risk factors for late effects because of sample size limitations. Analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient and Transplantation Characteristics

Patient and transplantation characteristics are presented in Table 1. Of the 325 patients eligible for analysis, 146 were children and 179 were adults. The median interval between the first and second transplantation was 17 months (range, 2 to 149 months) and 24 months (range, 2 to 158 months) for children and adults, respectively. The majority of children (74%) were in CR before second HCT, compared with 49% of adults. Children received a myeloablative conditioning regimen in 89% of first and 62% of second transplantations. The corresponding values for adults were 79% of first and 45% of second transplantations. Of those who received a myeloablative regimen in the first HCT, 61% of children and 44% of adults had a myeloablative regimen with second transplantation. Total body irradiation was used in the conditioning regimen in 45% of first and 40% of second pediatric and in 55% and 25% of adult transplantations. No conditioning agent or radiation was used with the second transplantation in 3% of children and 7% of adult patients. The median follow-up after second transplantation among both children and adult survivors was 72 months (range, 17 to 219 and 12 to 288 months, respectively).

Survival, Nonrelapse Mortality, and Relapse Outcomes

Among the 1-year survivors included in our study, 2- and 10-year conditional survival rates were 83% (95% confidence interval [CI], 77% to 89%) and 55% (95% CI, 44% to 65%) among children and 75% (95% CI, 69% to 81%) and 39% (95% CI, 31% to 48%) among adults (Table 2, Figure 1). Cumulative incidence of nonrelapse mortality among children was 4% and 10% at 2 years and 10 years, respectively (Table 2, Figure 2). The corresponding figures among adults were 15% and 34%, respectively. The cumulative incidence of relapse at 2 years and 10 years was 21% and 34% in children and 15% and 32% in adults, respectively (Table 2, Figure 3). Disease progression or relapse was the major cause of death (43 of 56 [77%] for children and 52 of 96 [54%] for adults). Overall causes of nonrelapse mortality included GVHD (32%), organ failure (25%), infection (16%), secondary malignancy (5%), and other/unknown cause (23%). The leading causes of nonrelapse mortality in children were GVHD (5%), organ failure (5%), and secondary malignancy (4%). The leading causes of nonrelapse mortality in adult patients were GVHD (16%), organ failure (11%), and infection (9%).

Table 2
Conditional Probability of Overall Survival and Cumulative Incidence of Nonrelapse Mortality and Relapse among One-Year Disease-Free Survivors after Second Allogeneic Hematopoietic Cell Transplantation

Outcomes	Children		Adults	
	Patients at Risk	% (95% CI)	Patients at Risk	% (95% CI)
Relapse				
2 Years	105	21 (15-28)	118	15 (10-20)
6 Years	47	34 (26-43)	49	27 (21-35)
10 Years	19	34 (26-43)	18	32 (24-40)
Nonrelapse mortality				
2 Years	105	4 (2-8)	118	15 (10-21)
6 Years	47	8 (4-14)	49	27 (20-34)
10 Years	19	10 (5-17)	18	34 (26-42)
Overall survival				
2 Years	118	83 (77-89)	133	75 (69-81)
6 Years	52	64 (55-72)	55	51 (43-58)
10 Years	18	55 (44-65)	22	39 (31-48)

95% CI indicates 95% confidence interval.

In proportional hazard models, disease status at the time of second HCT was the only independent predictor for overall mortality. The overall survival at 5 years for patients who were in CR at the time of the second transplantation was 66% (95% CI, 59% to 73%) compared with 48% (95% CI, 38% to 58%) for those not in remission at the time of transplantation. Compared with patients who were in CR, patients with active disease had significantly higher risks for overall mortality (hazard ratio, 1.71; 95% CI, 1.22 to 2.38; $P = .0017$).

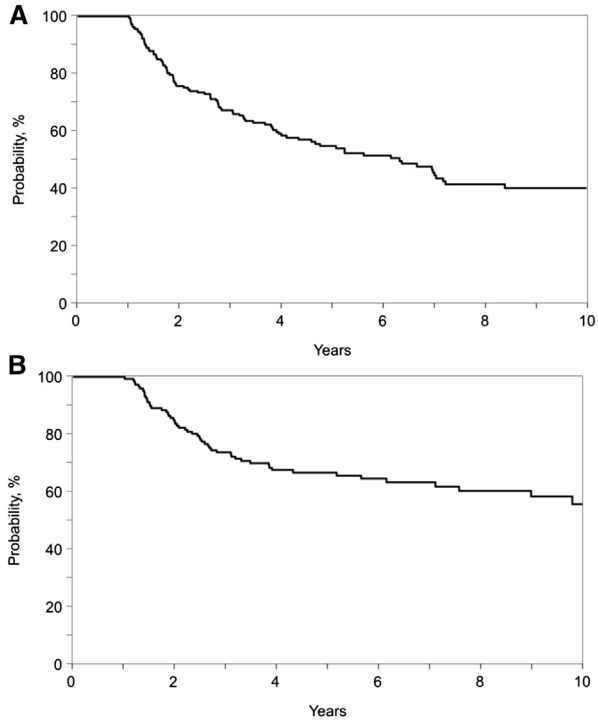

Figure 1. Overall survival among 1-year disease-free survivors of second allogeneic transplantation for acute myeloid leukemia, acute lymphoblastic leukemia, JMML, and MDS: (A) adult patients (age ≥18 years at second transplantation), and (B) children (age <18 years at second transplantation).

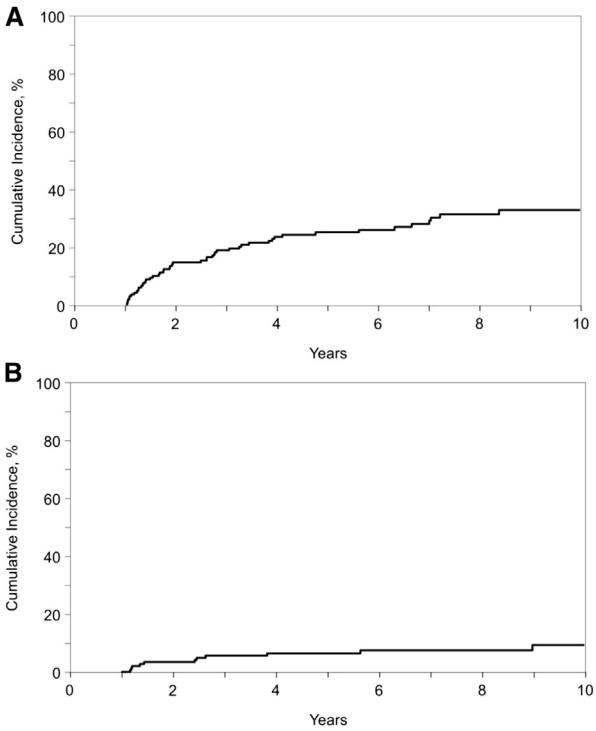

Figure 2. Nonrelapse mortality among 1-year disease-free survivors of second allogeneic transplantation for acute myeloid leukemia, acute lymphoblastic leukemia, JMML and MDS: (A) adult patients (age ≥18 years at second transplantation), and (B) children (age <18 years at second transplantation).

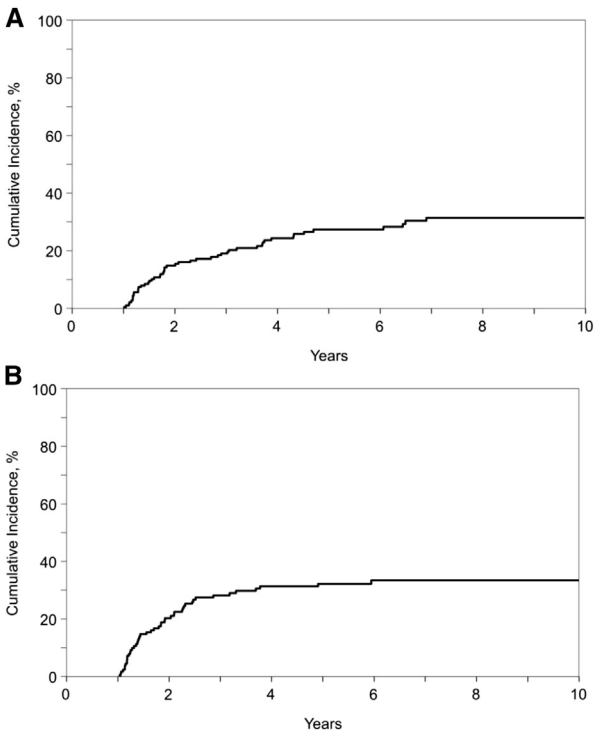

Figure 3. Relapse among 1-year disease-free survivors of second allogeneic transplantation for acute myeloid leukemia, acute lymphoblastic leukemia, JMML and MDS: (A) adult patients (age ≥18 years at second transplantation), and (B) children (age <18 years at second transplantation).

Late Effects and GVHD

Between first and second allogeneic HCT, at least 1 late effect was reported in 12% of patients. The most common reported late effects in children were stroke/seizures (3%) and growth disturbance (3%). Gonadal dysfunction (5%) and cataracts (5%) were the most frequently reported late effects among adults. Grade 2 to 4 acute GVHD was reported after the first allogeneic transplantation in 30% of children and 26% of adults. Grade 2 to 4 acute GVHD was diagnosed after the second transplantation in 47% of children and 46% of adults. Chronic GVHD requiring treatment was reported before the second transplantation in 16% and 32% of children and adults, respectively. New onset chronic GVHD requiring treatment was diagnosed after the second transplantation in 43% of children and 75% of adults. Data regarding the status or severity of chronic GVHD are not uniformly reported by centers to the CIBMTR database and these data are not presented.

The cumulative incidence of developing any late effect at 2 years and 10 years after second HCT was 42% (95% CI, 32% to 52%) and 63% (95% CI, 53% to 73%) among children and 45% (95% CI, 36% to 54%) and 55% (95% CI, 46% to 64%) among adults, respectively. The cumulative incidences of specific late effects are reported in Table 3. Ten years after second transplantation, the incidence was >10% for gonadal dysfunction, cataracts, growth hormone deficiency/growth disturbance, and hypothyroidism in pediatric survivors. Only avascular necrosis and cataracts were reported with an incidence greater than 10% in adult survivors. The 10-year cumulative incidence of a second cancer after second transplantation was 1% (95% CI, 0 to 4%) in pediatric and 8% (95% CI, 4% to 13%) in adult survivors. The primary sites for second cancers included nonmelanoma skin cancer (n = 9), oral cavity (n = 2), sarcoma (n = 2), skin melanoma (n = 1), and gastrointestinal tract (n = 1). In addition, 1 patient had post-transplantation lymphoproliferative disorder and 2 patients were reported to have squamous cell cancers of unknown site (the primary site could not be confirmed by the transplantation center).

DISCUSSION

In the present era, with several advances in post-transplantation supportive care practices, it is not unusual for a second allogeneic transplantation to be considered as treatment for patients whose disease relapses or progresses after a first allogeneic transplantation. We present the outcomes of a relatively large cohort of patients reported to the CIBMTR who received a second allogeneic transplantation for disease relapse and had survived in remission for at least 1 year. By focusing on long-term survival and late effects in this population, our study addresses important gaps in the literature. Our findings will inform the medical decision making of transplantation providers as they consider a second allogeneic transplantation in patients with relapsed acute leukemia and MDS.

There were several key findings in our analysis. First, we show that the majority of recipients of second allogeneic transplantations relapsed or died within the first year (74% in our study), confirming earlier results from smaller studies [1,2,15,23,24]. Second, we have shown that disease status at the time of second transplantation was the most important predictor of subsequent long-term survival. Patients in CR at the time of second transplantation had higher survival chances than those who were not in CR. Also, although considering the very high-risk nature of their disease, a

Table 3
Late Effects among One-Year Disease-Free Survivors after Second Allogeneic Hematopoietic Cell Transplantation

Patient and Transplantation Characteristics	Age Group at Second Transplantation					
	Children (≤18 years)			Adults (>18 years)		
	Rate before Second HCT* n (%)	CI at 2 years† % (95% CI)	CI at 10 years† % (95% CI)	Rate before Second HCT* n (%)	CI at 2 years† % (95% CI)	CI at 10 years† % (95% CI)
Seizure/stroke	4 (3)	4 (1-7)	4 (2-8)	2 (1)	0	1 (0-2)
Myocardial infarction	0	0	0	0	1 (0-2)	1 (0-2)
Gonadal dysfunction	3 (2)	6 (3-11)	16 (10-23)	9 (5)	4 (2-7)	5 (2-8)
Renal failure	1 (1)	1 (0-4)	4 (1-8)	2 (1)	3 (1-6)	4 (1-7)
Avascular necrosis	2 (1)	4 (2-8)	5 (2-9)	4 (2)	10 (6-15)	13 (9-19)
Cataracts	1 (1)	9 (4-14)	20 (13-28)	9 (5)	14 (9-20)	20 (14-26)
Growth hormone deficiency/growth failure	4 (3)	8 (4-14)	22 (15-30)	0	0	0
Hypothyroidism	1 (1)	7 (3-12)	13 (7-20)	2 (1)	2 (1-5)	4 (1-7)
Cirrhosis	0	0	0	0	0	0
Bronchiolitis obliterans	0	3 (1-7)	4 (1-8)	1 (1)	4 (2-8)	4 (2-8)
Second cancers	0	1 (0-3)	1 (0-4)	2 (1)	1 (0-3)	8 (4-13)

CI indicates cumulative incidence.
* Rate of late effects after first allogeneic transplantation, but before second transplantation (censored at time of second transplantation).
† Cumulative incidence estimates.

substantial number of patients who were alive and disease free at 1 year after their second transplantation continued to survive on long-term (up to 10 years) follow-up. However, relapse continued to be the major cause of treatment failure, even among the disease-free survivors beyond the first year after second transplantation. Finally, a relatively large proportion of second transplantation survivors suffered from long-term toxicities.

Overall survival for patients who survived the first year after their second transplantation was favorable at 2 years (83% in children and 75% in adults). Overall survival gradually declined before stabilizing between years 7 and 8 with overall survival at 10 years of 55% in children and 39% in adults. Disease relapse or progression was the leading cause of mortality after second transplantation and accounted for 77% and 52% of deaths in children and adults, respectively. This is consistent with the published literature of all patients after second HCT [1,9,15,17,25]. As expected, nonrelapse mortality rates were generally lower for children compared with for adults [1,9,15,25].

Disease status in remission and longer duration between first transplantation and relapse and second HCT are the most consistent factors influencing survival after second HCT across multiple studies [3,5,11,15,17,26]. We evaluated these factors, as well as other published potential prognostic factors, including diagnosis, patient age, disease status at first HCT, donor pairing at first and second HCT, GVHD after first transplantation, and conditioning intensity at second HCT [1-3,9,24,27,28]. Stem cell source was not evaluated as there were insufficient patients in each group to draw conclusions. Remission status was the only factor predictive of survival after second transplantation in our study. Similar to other studies, patients in CR had a survival advantage compared with those who underwent transplantation with active disease [15,17,24,26,29]. This finding supports the use of additional therapy, if feasible, to achieve CR before second HCT for patients with relapsed acute leukemia and MDS to maximize the potential for long-term survival. Patients with disease relapse after a first allogeneic HCT should be encouraged to participate in clinical trials of novel treatment approaches [30].

We did not find an association of donor switching between first and second transplantation and overall survival. This may be explained by the relatively small number of donor-recipient pairs in each of the groups analyzed (related-related versus related-unrelated versus unrelated-unrelated [same donor] versus unrelated-unrelated [different donor] versus other). Some prior investigations were similarly restricted in their ability to detect a survival difference attributable to change in donor pairing due to limited sample size. However, the results of this and prior studies do not support the strategy of changing donors between first and second transplantation in an effort to improve overall survival [1,2,11,15,25]. When comparing the results of our study with published literature, it is worth noting that survival and risk factor analyses in prior studies included all patients, regardless of survival since transplantation, whereas we focused only on those who survived disease free for the initial post-transplantation year. This may explain why the time between first and second HCT was not predictive of survival, as patients with shorter duration between transplantations may have relapsed or died during the first year.

We report the cumulative incidence of developing at least a single late effect at 10 years after second HCT of 63% in children and 55% in adult patients. The cumulative incidence of late effects between 2 and 10 years did not increase substantially in adults. The increase in the cumulative incidence of late effects in children between 2 and 10 years was primarily due to gonadal failure. The median age of 9 years indicates that many of the patients were prepubertal at the time of second transplantation. The cumulative incidences of late effects presented are similar to what is described in the literature in long-term survivors of single transplantation. Patients in the Bone Marrow Transplant Survivor Study reported at least 1 chronic health condition in 32% to 38.2% of 2-year survivors and in 74% of 10-year survivors of first transplantation for leukemia and aplastic anemia [20,21,31]. This is also comparable to the 79% of 145 pediatric survivors of single transplantation followed for a median of 11 years and lower than the 91% found in 99 Australian patients followed for a median of 74 months after first HCT [19,32]. The specific late effects evaluated differ in each of the studies referenced. However, the categories of conditions investigated are similar and reasonably allow for comparison between studies. CIBMTR data forms capture a limited number of late complications, and hence, we may have underestimated the true incidence of late effects in second

allogeneic transplantation survivors. Regardless, our study emphasizes the need for continued long-term surveillance for late effects in this population [33,34].

We acknowledge several limitations to our retrospective cohort study. First, there is the potential for selection bias at the level of the individual centers regarding which patients are offered a second transplantation (eg, patients may be more likely to receive a second transplantation if they have fewer comorbidities, better performance status, absence of severe GVHD, and longer time between first transplantation and relapse). As noted above, data were collected on selected late effects. Capture of long-term follow-up information by transplantation centers for their transplant recipients can be challenging. However, our follow-up information was robust with a completeness index of follow-up (ratio of observed versus expected follow-up for the cohort) of 94% at 5 years and 83% at 10 years after second transplantation. Screening practices can differ between institutions, resulting in potential under-reporting of specific effects. The median follow-up of our cohort was approximately 6 years. Although this is an acceptable period of time, it is possible that a longer duration of follow-up may result in an increase in the number of reported late effects. Finally, even though our study is the largest to date, the number of patients included and the number of post-transplantation events were still relatively small and future studies will have to readdress this issue in larger patient cohorts. On the same note, the number of umbilical cord blood recipients was small and outcomes with second transplantations using this graft source will have to be characterized in larger studies.

In summary, the 1-year overall survival after second allogeneic transplantation for relapsed acute leukemia and MDS is suboptimal. However, many patients who live disease-free for at least 1 year after second transplantation can be expected to survive long term and their survival is best optimized when patients receive a second transplantation while in CR. The majority of late failures are due to relapse and late effects are frequently encountered. Future trials focusing on reducing risks of relapse, novel treatments for treating post-transplantation relapse, and implementing systematic surveillance for long-term toxicities in this population are warranted.

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